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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,084	03/07/2002	Clarence Webster Andrews III	PU3517USW	7283

23347 7590 07/26/2005

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,084	ANDREWS ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,9-14,18-20,23,25,26,28,29,34-36,40,43-51 and 54-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23,25 and 55* is/are allowed.

6)☒ Claim(s) *2-7,9-14,18-20,26,28,29,34-36,40,43-51,54 and 56-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05132005* & 03162005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 13, 2005 has been entered.

Claims 2-7, 9-14, 18-20, 23, 25, 26, 28, 29, 34-36, 40, 43-51 and 54-62 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 18 recites that "R^7 is C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, -NH_2, or heterocycle" wherein the recitation 'C_{1-8}alkyl optionally substituted with –NH_2' lacks support in the originally filed disclosure. The

definition for R^7 provided in the specification page 14, lines 27-29 is different and does not include $-NH_2$ in the optional substituent list intended for alkyl.

Claims 28, 29, 48, 49, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of an HIV-1 infection or a method of inhibiting HIV-1 reverse transcriptase, does not reasonably provide enablement for a method of treatment of HIV infection generally or a method of inhibiting HIV reverse transcriptase generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The scope of the claims is not adequately enabled solely based on the activity related to HIV-**1** reverse transcriptase inhibitory activity provided in the specification. First, the instant claims cover diseases due to all types of HIV infections, i.e., caused by HIV-1, HIV-2, etc. that are known to exist and those that may be discovered in the future, for which there is no

enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents having HIV-1 reverse transcriptase inhibitory activity, useful to treat all types of viral infections, which include AIDS, etc. Test procedures and assays are provided in the specification at pages 391-396 and IC_{50} values for some of the exemplified compounds are provided in Table 1, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of all types of viral infections embraced the instant claims. One of ordinary skill would not know to extrapolate this test data to compounds having the assorted types of substituents provided in the instant claims. The disorders encompassed by the instant claims include AIDS, etc., some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

State of the art references provide that:

(1) http://www.hivguidelines.org/public_html/center/clinical-education/q-and-a/hiv-2.htm

Little is known to date about the effectiveness of current antiretroviral medications against HIV-2 infection, in part, because antiretroviral medications have not been widely available in areas with large numbers of HIV-2 infection. Little is known about whether the current emphasis on early initiation of combination antiretroviral therapy for HIV-1 is appropriate for treatment of HIV-2. Viral load testing, which has become an important tool in treatment planning and monitoring for HIV-1 is not currently available for HIV-2.

(2) http://www.aegis.com/aidsline/1992/nov/M92B0027.html

Calanolides A (1) and B (4) were completely protective against HIV-1 replication and cytopathicity (EC50 values of 0.1 microM and 0.4 microM, respectively), but were inactive against HIV-2.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

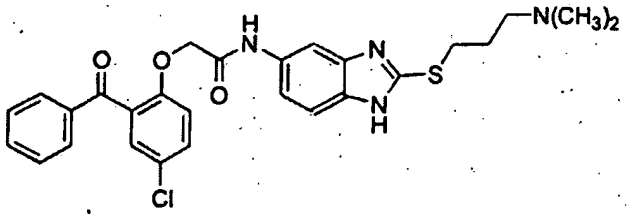
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-7, 9-14, 18-20, 26, 28, 29, 34-36, 40, 43-51, 54 and 56-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 2, when R^4 is heterocycle, among the optional substituent list, the term "-$SR^{10}N(R^{10})_2$" is not understood. It is not clear whether the $-N(R^{10})_2$ is attached to the 'alkyl' group of R^{10} or directly to S, in which case the sulfur atom becomes trivalent and therefore requires a counter ion which has not been defined for the compounds. The discrepancy is also observed in claim 12 (see page 8, line 8).

This rejection was made previously and applicant indicated that "An illustration of the term "-$SR^{10}N(R^{10})_2$" is provided by Example 71, page 145" (see response filed July 28, 2004). The structural formula of Example 71 is depicted below for convenience:

Example 71:



In the claims, R^{10} is defined to represent a monovalent group, i.e., C_{1-8} alkyl. In the above structure S and $N(CH_3)_2$ are connected by an alkylene chain containing 3 carbons which is a bivalent group. This is confusing and not understood how the same moiety can be a monovalent as well as a bivalent group. In the above term the same variable is used as a linking moiety as well as a monovalent substituent, which leads to ambiguity in properly interpreting and understanding the metes and bounds of the claim.

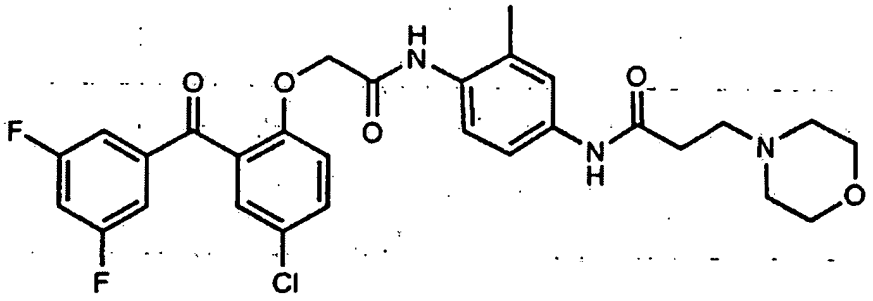
2. In claim 2, the recitation "R^7 is C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of hydroxy;" is confusing because following 'selected from the group consisting of' there is only one term. The other terms are separated by " ; " and therefore, are understood as definition for R^7 and not part of the substituent list. Appropriate correction is required.

3. In claim 2, when R^4 is aryl, in the list of substituents, the term "-$NC(O)R^{11}$" has the nitrogen with an open valency. It is not clear what is intended to be substituted on the nitrogen.

The discrepancy is also observed in other claims, see e.g,, claim 6 (see page 5, line 1); claim 10 (page 7, line 3), etc.

This rejection was made previously and applicant indicated that "An illustration of the term "-NC(O)R^{11}" is provided by Example 122, page 208" (see response filed on July 28, 2004). The structure of Example 122 is provided below for convenience:

Example 122



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It appears that applicant is indicating that the open valency of the nitrogen is filled by H, however, in the absence of specific recitation in the claim, such assumption cannot be generally made. Applicant must provide clear definitions for each term in the claim properly supported by the disclosure. Similar terms are found throughout the claims, see e.g., claim 3, the term "-$NS(O)_2R^7$" wherein the nitrogen has an open valency.

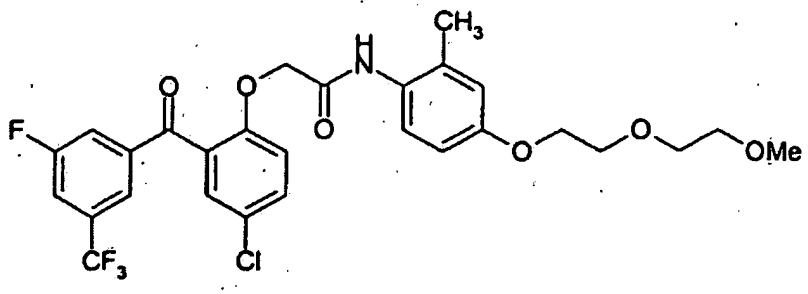
4. In claim 6, X is defined to be "C, O or N" wherein the carbon and the nitrogen have open valencies. It is not clear what other substituents are intended to satisfy the open valency. The discrepancy is also observed in other claims, see e.g., claim 10 (see line 4); claim 12 (line 4), etc.

This rejection was made previously and applicant indicated that "one of ordinary skill in the art would understand that open valencies are filled with hydrogen. Illustrations of writing

structures in this way are provided in the Examples" (see response filed July 28, 2004). This argument is not persuasive. While the Examples in the specification provide the groups $-CH_2-$ or –NH- in place of X in the structural formula, there is no specific recitation of these groups in the claim. The claims at present contain terms with open valency and there is no guidance that the open valencies are always filled only with H. As recited the terms are open to any type of link such as =CH-, or a carbene, etc. Applicant must provide clear definitions for each term in the claim properly supported by the disclosure.

5. In claim 10, under the substituent list on aryl group of R^4, the term "$-OR^{11}OR^{11}$" (see page 7, line 2) is not understood. The list already consists of "$-OR^{11}$" (see the term immediately before the above term in question on line 2 of page 7). The discrepancy is also observed in claim 17.

This rejection was made previously and applicant indicated that "An illustration of the term "$-OR^{11}OR^{11}$" is provided by Examples 250, 251 and 252 on pages 359-361" (see response filed on July 24, 2005). The structure of Example 250 is provided below for convenience:



In the claims, R^{11} is defined to represent a monovalent group, e.g., C_{1-8} alkyl. In the above structure O and $O(CH_2)_2$-OMe are connected by an alkylene chain containing 2 carbons which is a bivalent group. This is confusing and not understood how the same moiety can be a

monovalent as well as a bivalent group. In the above term the same variable is used as a linking moiety as well as a monovalent substituent, which leads to ambiguity in properly interpreting and understanding the metes and bounds of the claim.

6. Claim 19 recites the limitation "R^7 is $-NH_2$" in line 5. There is insufficient antecedent basis for this limitation in claim 18 on which claim 19 is dependent. Claim 18 defines R^7 to be "C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxyl, $-NH_2$, or heterocycle" and the definition does not provide that 'R^7 is $-NH_2$'.

7. Claim 26 recites 'R^1 is C_{6-14} aryl substituted in the meta position, **particularly** with halogen' wherein the use of the term "particularly" is indefinite. It is not understood if any other substituents are intended here. The discrepancy is also found in claims 43-47.

8. In claim 40, it is recited "R^3 is hydrogen" (see page 20, last line), however, the structural formula does not contain R^3.

9. Claim 48 drawn to 'a method of treatment of an HIV infection', recites 'an **antivirally** effective amount of the compound', wherein the recitation 'antivirally' is broader than the intended treatment of HIV infection. Similar discrepancy is also observed in claim 49. Applicant's attention is directed to claim 28, which appropriately recites the corresponding effective amount.

Allowable Subject Matter

Claims 23, 25 and 55 are allowed. The references of record do not teach or fairly suggest the claimed compounds.

Receipt is acknowledged of the Information Disclosure Statements filed on March 16 and May 13, 2005 and a copies are enclosed herewith. The International Search Report for Hungarian Patent Application No. P0202593 is also acknowledged and the cited document has been fully considered. The citation of the search report was removed from PTO 1449 (by drawing a line through) because the "International Search Report" itself is not a proper publication *per se* that complies with the requirements of 37 CFR 1.97 and 1.98 and therefore, will not appear on the patent as a cited document.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

July 25, 2005